National Institute for Health and Care Excellence

Final

Maternal and child nutrition

[B] Evidence reviews for optimum folic acid supplementation dose before and during the first 12 weeks of pregnancy for those with a BMI 25 kg/m2 or more

NICE guideline NG247

Evidence reviews underpinning recommendation 1.1.6 and 1.1.8 in the NICE guideline

January 2025

Final

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Optimum folic acid supplementation dose before and during the first 12 weeks of pregnancy for those with a BMI ≥ 25 kg/m^2 or more

Review question

What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women with a BMI ≥ 25 kg/m^2 or more?

Introduction

In 2010, the Royal College of Obstetricians and Gynaecologists (RCOG) advised that women medically classified as obese (BMI ≥30 kg/m^2) who are planning pregnancy or are pregnant should take a high dose of folic acid supplements (5mg) to reduce the risk of neural tube defects (NTDs) in babies. There is a higher prevalence of NTDs in babies in this population. The RCOG guidance was based on evidence extrapolated from studies in women with known pre-gestational risk factors for NTDs, and not from evidence for the benefit of high dose folic acid in pregnant women with obesity. As a significant period of time has passed since this recommendation was introduced, this evidence review will provide an opportunity to assess the effectiveness of high dose folic acid supplementation and to determine if there are preventative benefits of the higher dose compared to standard dose folic acid in those with a BMI in the overweight or obese categories >25 kg/m^2. Specifically, the aim of this evidence review is to determine what dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed to prevent NTDs, other folate sensitive congenital defects and pregnancy outcomes reported to be associated with folate insufficiency in women with a pre-pregnancy BMI in the overweight or obese category (≥25 kg/m^2).

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women in the preconception stage trying to become pregnant or during the first 12 weeks of a single or multiple pregnancy, who have a BMI of 25 kg/m^2 or more
Intervention	• Low-dose folic acid supplementation (<1 mg daily) • Medium-dose folic acid supplementation (≥1 to <5 mg daily) • High-dose folic acid supplementation (≥5 mg daily) In combination or not with other vitamins and minerals.
Comparison	• A different folic acid supplementation dose • Standard care (as defined by the study) • Placebo • No intervention
Outcome	**Critical:** • neural tube defects • birthweight

	• hypertensive disorders of pregnancy (preeclampsia and gestational hypertension) **Important:** • red blood cell folate concentrations • neurodevelopmental delay (dichotomous outcome, not continuous outcomes such as mean change in score): - severe (score of >2SD below normal on validated assessment scales, or Bayley assessment scale of mental development index [MDI] or psychomotor developmental index [PDI]) - moderate (score of 1-2 SD below normal on validated assessment scales, or Bayley assessment scale MDI or PDI 70-84) • congenital heart defects • midline facial defects such as cleft lip or cleft palate

BMI: body mass index; mg: milligrams; SD: standard deviation

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Two prospective cohort studies were included in this review (Catov 2009, Martinussen 2015).

The included studies are summarised in Table 2.

One study compared 200µg daily folic acid (in multivitamin supplementation) to no intervention (Catov 2009) and 1 study compared >200µg daily folic acid supplementation to <200µg daily folic acid supplementation (Martinussen 2015). Both studies assessed low dose folic acid supplementation.

There was no evidence identified for medium dose (≥1 to <5 mg daily) and high dose folic acid supplementations (≥5 mg daily).

Both the studies (Catov 2009, Martinussen 2015) were in women with singleton pregnancies who took folic acid supplementation during the periconceptional period. One study was conducted in Denmark (Catov 2009), and 1 study was conducted in the United States of America (Martinussen 2015).

Evidence was only available for the outcome preeclampsia. There was no evidence available for the following outcomes: neural tube defects, birthweight, red blood cell folate concentrations, neurodevelopmental delay, congenital heart defects and midline facial defects such as cleft lip or cleft palate.

As per protocol the evidence was stratified according to body mass index (BMI) thresholds on booking (overweight range: 25 to 29.99 kg/m^2; obesity range 1: 30 to 34.99 kg/m^2; obesity range 2: 35 to 39.99 kg/m^2; obesity range 3: >40 kg/m^2). There was no sufficient evidence to stratify evidence based on women with gestational diabetes or pre-existing diabetes (type 1 and type 2), or single versus multiple pregnancies.

As per protocol, subgroup analyses for the following groups were to be conducted if there was heterogeneity: deprived socioeconomic group, women and parents with disabilities, including learning disabilities and other physical and mental health conditions, women going through assisted conception, religion, cultural considerations and ethnicity. There was no heterogeneity identified in the evidence, hence subgroup analysis was not conducted.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Catov 2005 Prospective cohort study Denmark	N=28601 women with singleton pregnancies who took folic acid supplementation during the periconceptional period Maternal age, years (%); mean (SD) - NR 200µg folic acid (in multivitamin supplementation): <21: 148 (0.8) 21–25: 2337 (12.6) 26–30: 8481 (45.7) 31–35: 5686 (30.7) ≥36: 1899 (10.2) No intervention: <21: 199 (2.6) 21–25 1251 (16.5) 26–30 3021 (39.8)	Folic acid 200µg daily (in multivitamin supplementation)	No intervention • (no multivitamin or folic acid supplementation) Non-users were women with a body mass index of 22 kg/ m^2.	• Preeclampsia (follow-up - gestational day 140 - date of delivery)	Covariates adjusted in the analysis: • Smoking • Parity • Chronic hypertension • Gestational age at recruitment Strata: BMI >25 kg/ m^2.

Study	Population	Intervention	Comparison	Outcomes	Comments
	31–35 2241 (29.6) ≥36 870 (11.5) Maternal BMI, kg/m^2, n (%); mean (SD) - NR 200µg folic acid (in multivitamin supplementation): <18.5: 801 (4.3) 18.5 - 24.9: 12621 (68.0) 25 - 29.9: 3544 (19.1) ≥30: 1585 (8.6) No intervention: <18.5: 324 (4.3) 18.5 - 24.9: 4734 (62.4) 25 - 29.9: 1677 (22.1) ≥30: 847 (11.2)				
Martinussen 2015 Prospective cohort study USA	N=3647 women with singleton pregnancies who took folic acid supplementation before and during the first three months of pregnancy Maternal age, years (%); mean (SD) - NR <20: 424 (11.6) 20≤25: 897 (24.6) 25≤30: 1117 (30.6)	Folic acid supplementation >200µg daily Mean folic acid intake in first trimester was defined as the average intake over these four months. For each month and for the first trimester overall, daily folic acid intake was divided into a dichotomous variable of use (no use: <200 µg daily and use: >200µg average use).	Folic acid supplementation <200µg daily	• Preeclampsia (folic acid started one month before conception) (follow-up first trimester of pregnancy to birth) • Preeclampsia (folic acid taken throughout first trimester) (follow-up first trimester of pregnancy to birth)	Covariates adjusted in the analysis: • Study (AIP or NIP) • Maternal age • Maternal ethnicity • Maternal education • Maternal marital status • Maternal smoking in pregnancy • Any miscarriages or stillbirths

Study	Population	Intervention	Comparison	Outcomes	Comments
	30≤35: 906 (24.9) ≥35: 302 (8.3) BMI, kg/m^2, n (%); mean (SD) - NR <25: 2431 (68.3) ≥25: 1128 (31.7)				in previous pregnancies Strata: BMI ≥25 kg/m^2.

AIP: Asthma in Pregnancy Study; BMI: body mass index; NR: not reported; NIP: Nutrition in Pregnancy Study; SD: standard deviation; µg: micrograms

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Folic acid supplementation 200µg/day (in multivitamin supplementation) versus no intervention (no multivitamin and folic acid supplementation) in women with BMI >25 kg/m^2 in singleton pregnancies who took folic acid supplementation during the periconceptional period

One study was included in this comparison.

Evidence showed that there was no important difference in risk of preeclampsia in women with BMI 26 kg/m^2 who took folic acid supplementation 200µg/day (in multivitamin supplementation) compared to women with BMI 22 kg/m^2 who did not take the supplementation. Evidence showed that in women with BMI 28 kg/m^2 and BMI 30 kg/m^2 there was important harm with a higher risk of preeclampsia associated with folic acid supplementation 200µg/day (in multivitamin supplementation) compared to women with BMI 22 kg/m^2 who did not take the supplementation.

The evidence ranged from low to moderate quality.

Folic acid supplementation >200µg/day versus folic acid supplementation <200µg/day in women with BMI ≥25 kg/m^2 in singleton pregnancies who took folic acid supplementation during the periconceptional period and during the first three months of pregnancy

One study was included in this comparison.

Evidence showed that in women with BMI ≥25 kg/m^2 (for both who started taking folic acid supplements one month before conception and those who took folic acid supplements throughout the first trimester of pregnancy), there was no important difference in risk of preeclampsia between folic acid supplementation >200µg/day and folic acid supplementation <200µg/day.

The evidence was very low quality.

See appendix F for full GRADE tables.

Economic evidence

Included studies

No economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

As the main aim of this review was to determine which folic acid supplementation dose women with a BMI≥25 kg/m^2 need before and during the first 12 weeks of pregnancy, the committee agreed to prioritise neural tube defects, birthweight and hypertensive disorders of pregnancy (preeclampsia and gestational hypertension) as critical outcomes because adequate concentrations of folic acid can reduce the risk of NTD, and there have been reported associations between low folic acid status and the others outcomes.

As important outcomes, the committee prioritised red blood cell folate concentration as this is a biomarker for folate status. Outcomes related to the baby, including neurodevelopmental delay, congenital heart defects and midline facial defects, were prioritised as important outcomes because folic acid reduces the risk of birth defects related to the brain and heart, and of midline facial defects such as cleft or lip palate.

Evidence was only available for the outcome pre-eclampsia. There was no evidence for the following outcomes: neural tube defects, birthweight, red blood cell folate concentrations, neurodevelopmental delay, congenital heart defects and midline facial defects such as cleft lip or cleft palate.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The quality of the evidence ranged from very low to moderate quality, and most evidence was very low or low quality. The main reasons for downgrading were risk of bias and imprecision of effect estimates (95% confidence intervals crossing decision making thresholds). Risk of bias was most commonly due to lack of clarity in differences between the groups at baseline, deviations from intended interventions, missing outcome data, and bias in measurement of outcomes as folic acid/multivitamin intake was patient self-reported.

Studies were assessed for quality using the Cochrane ROBINS-I tool.

Benefits and harms

Overall, the committee considered that the evidence was very limited and uninformative. There was limited low-quality evidence available on low dose folic acid (200µg) in women with singleton pregnancies with a BMI of ≥25 kg/m^2 (the recommended dose before and during first 12 weeks of pregnancy for the general population is 400µg). The evidence for

folic acid supplementation did not show benefit for the outcome of preeclampsia in women medically classified as overweight or obese. One study which showed reduced risk of preeclampsia when taking a multivitamin supplement including low dose of folic acid in women with weight within the healthy BMI range, reported a higher risk of preeclampsia for those with BMI 28kg/m^2 and BMI 30 kg/m^2, when compared to the reference group of non-users of multivitamins with BMI of 22 kg/m^2, but the committee noted that the risk was comparable to non-users with the same BMI. Because there is a recognised relationship between maternal overweight and obesity with preeclampsia risk this study could imply that the folic acid dose in most multivitamin supplements (usually 200µg) is inadequate to prevent preeclampsia in women medically classified as overweight or obese. There was no evidence for any other relevant outcomes, including NTDs. The committee also acknowledged the lack of evidence for medium and high dose folic acid for this group.

The committee discussed that the current advice for those with ≥BMI 30 kg/m^2 to take high dose of folic acid (5mg), and not the standard dose of 400µg, is not evidence-based and the higher incidence of babies with neural tube defects among this population may be unrelated to folate insufficiency, and could be the consequence of unrelated metabolic disorders. The committee discussed that there is no evidence of harm from high dose folic acid but no evidence of benefit either. Therefore, the committee agreed that without evidence to support a high dose in this population, this should not be recommended. While the advice has been for those with BMI ≥30 kg/m^2, also people in the overweight category (BMI 25.0-29.9kg/m^2), for whom there is minimal evidence for increased risk of NTDs, may be aware of the advice about the high dose of 5mg so the committee agreed that people with BMI ≥25kg/m^2 should be reassured that they do not need to take more than the standard 400µg of folic acid unless they have any of the known risk factors such as history of neural tube defects or diabetes.

All available evidence was in those with single pregnancies. There was no evidence for women with multiple pregnancies, hence the committee did not make any specific recommendations for this group. The committee referred to the section on diet, lifestyle and nutritional supplements in the NICE guideline on Twin and triplet pregnancy, as this provides advice on nutritional supplements including folic acid for multiple pregnancies.

Due to lack of evidence for women with a BMI of ≥25 kg/m^2, the committee included this population in the research recommendation on high-dose of folic acid (5mg). See Appendix K in evidence review A for more details. The committee discussed that those who have had bariatric surgery may need specialist advice around folic acid and other micronutrients before and during pregnancy so agreed, based on consensus, that they should be advised to contact their bariatric surgery unit for individualised, specialist advice because of potential metabolic changes after such surgery. This aligns with the British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery, which states that those who become pregnant after a bariatric surgery should be considered a specialist obstetric population with specific needs, including access to specialist dietetic support and close monitoring of nutrition (O'Kane 2020).

Cost effectiveness and resource use

No economic evidence was identified for this review. The recommendation should incur no resource implications, as 400µg of folic acid is current practice for women in the general population planning a pregnancy or being pregnant. The recommendation to advise those who have undergone bariatric surgery and are planning a pregnancy or are pregnant to contact their bariatric surgery unit for individualised, specialist advice about folic acid and other micronutrients reflects current best practice. However, it is noted that this may not be routine practice in some areas and therefore might lead to resource implications.

Other factors the committee took into account

For this review question, the population in the evidence was women and no evidence was identified or reviewed for trans men or non-binary people. The protocol and literature searches were not designed to specifically look for evidence on trans men or non-binary people but they were also not excluded. However, there is a small chance evidence on them may not have been captured, if such evidence exists. In discussing the evidence, the committee considered whether the recommendations could apply to a broader population, and used gender inclusive language to promote equity, respect and effective communication with everyone. Healthcare professionals should use their clinical judgement when implementing the recommendations, taking into account each person's circumstances, needs and preferences, and ensuring all people are treated with dignity and respect throughout their care.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.6 and 1.1.8.

References – included studies

Effectiveness

Catov 2009

Catov, J. M., Nohr, E. A., Bodnar, L. M. et al. (2009) Association of periconceptional multivitamin use with reduced risk of preeclampsia among normal-weight women in the Danish National Birth Cohort. American Journal of Epidemiology 169(11): 1304-11

Martinussen 2015

Martinussen, M. P., Bracken, M. B., Triche, E. W. et al. (2015) Folic acid supplementation in early pregnancy and the risk of preeclampsia, small for gestational age offspring and preterm delivery. European Journal of Obstetrics, Gynaecology, & Reproductive Biology 195: 94-9

Other

O'Kane 2020

O'Kane M, Parretti HM, Pinkney J, et al. British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery—2020 update. Obesity Reviews. 2020; 21:e13087.

Appendices

Appendix A Review protocol

Review protocol for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42022336450
Review title	Optimum folic acid supplementation dose before and during the first 12 weeks of pregnancy for women with a BMI ≥ 25 kg/m^2 or more
Review question	What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?
Objective	To determine the optimal folic acid supplementation dose before and during the first 12 weeks of pregnancy for women a BMI ≥ 25 kg/m^2 or more.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database (INAHTA) • Epistemonikos Searches will be restricted by: • English language only • human studies only.

Field	Content
	The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Folic acid supplementation for women with a BMI ≥ 25 kg/m^2 or more.
Population	• Women in the preconception stage trying to become pregnant or during the first 12 weeks of a single or multiple pregnancy, who have a BMI of 25 kg/m^2 or more. *If any study or systematic review includes <1/3 of women with a BMI <25 kg/m^2, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.*
Intervention	• Low-dose folic acid supplementation (<1 mg daily) • Medium-dose folic acid supplementation (≥1 to <5 mg daily) • High-dose folic acid supplementation (≥5 mg daily) In combination or not with other vitamins and minerals.
Comparator	• A different folic acid supplementation dose • Standard care (as defined by the study) • Placebo • No intervention

Types of study to be included	Include published full-text papers:
	• systematic reviews of RCTs
	• parallel RCTs
	• if insufficient parallel RCTs*:
	  ○ quasi-randomised controlled trials
	  ○ non-randomised controlled trials/prospective cohort studies
	  ○ retrospective cohort studies
	  ○ historically controlled studies.
	
	*Non-randomised studies will be considered for inclusion if insufficient RCT evidence is available for guideline decision making. Sufficiency will be judged taking into account factors including

Field	Content
	number/quality/sample size of RCTs, outcomes reported and availability of data from subgroups of interest. Non-randomised studies will only be included if they adjust for cofounding factors in the analysis. Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	Setting: • countries other than high income countries (as defined by the OECD). *If any study or systematic review includes <1/3 of women who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.*
Context	The population of this guideline may overlap with the population of women included in other NICE guidelines (such as postnatal care, antenatal care, intrapartum care, pregnancy and complex social factors or obesity prevention).
Primary outcomes (critical outcomes)	• Neural tube defects (NTDs) • Birthweight • Hypertensive disorders of pregnancy (preeclampsia and gestational hypertension)
Secondary outcomes (important outcomes)	• Red blood cell (RBC) folate concentrations • Neurodevelopmental delay (dichotomous outcome, not continuous outcomes such as mean change in score): - severe (score of >2SD below normal on validated assessment scales, or Bayley assessment scale of mental development index [MDI] or psychomotor developmental index [PDI]) - moderate (score of 1-2 SD below normal on validated assessment scales, or Bayley assessment scale MDI or PDI 70-84) • Congenital heart defects • Midline facial defects such as cleft lip or cleft palate

Field	Content
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled.

Field	Content
	The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • NTDs, hypertensive disorders of pregnancy, neurodevelopmental outcomes, congenital heart defects, cleft palate: statistical significance • validated scales/continuous outcomes: published MIDs where available • all other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes.

Analysis of subgroups	Evidence will be stratified by:
	• women with gestational diabetes/pre-existing diabetes (type 1 and type 2)
	• single versus multiple pregnancies
	• BMI thresholds on booking:
	  ○ Overweight range: 25 to 29.99 kg/m^2
	  ○ Obesity range 1: 30 to 34.99 kg/m^2
	  ○ Obesity range 2: 35 to 39.99 kg/m^2
	  ○ Obesity range 3: >40 kg/m^2.
	
	Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
	• deprived socioeconomic group
	• women and parents with disabilities, including learning disabilities and other physical and mental health conditions
	• women going through assisted conception
	• religion and cultural considerations
	• ethnicity
	  ○ White/White British
	  ○ Asian/Asian British

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Black/African/Caribbean/Black British
Mixed/Multiple ethnic groups
other ethnic group.

Where evidence is stratified or sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.
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☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)
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<tr><td>Review team members</td><td>• Senior Systematic Reviewer
• Systematic Reviewer</td></tr>
<tr><td>Funding sources/sponsor</td><td>This systematic review is being completed by the National Institute for Health and Care Excellence</td></tr>
<tr><td>Conflicts of interest</td><td>All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of</td></tr>
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Field	Content
	interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10191
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=336450
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Folic acid, pregnancy, overweight, obesity
Details of existing review of same topic by same authors	Not applicable
Current review status	☐ Ongoing ☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
Additional information	None
Details of final publication	www.nice.org.uk

BMI: body mass index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; EPPI: Evidence for Policy & Practice Information; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; m: metre; MID: minimally important difference; mg: milligrams; NGA: National Guideline Alliance; NHS: National health service; NICE: National

Institute for Health and Care Excellence; OECD: Organization for Economic Cooperation and Development; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions.

Appendix B Literature search strategies

Literature search strategies for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Effectiveness searches

Database: Medline

Date of last search: 04/12/2023

#	Searches
1	exp Pregnancy/ or Pregnant Women/ or Prenatal Care/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	Preconception Care/
5	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	adiposity/ or body mass index/ or body size/ or body weight/ or overweight/ or obesity/ or obesity, abdominal/ or obesity, maternal/ or obesity, metabolically benign/ or obesity, morbid/ or waist circumference/ or waist-hip ratio/ or waist-height ratio/ or weight gain/ or skinfold thickness/ or body fat distribution/
11	exp Adipose Tissue/
12	(obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos* or (weight adj2 (manag* or gain* or increas* or excess or chang*))).ti,ab,kf.
13	(body mass index or BMI or quetelet index).ti,ab,kf.
14	(waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*).ti,ab,kf.
15	(skin fold* or skinfold* or body composition or (body fat adj3 percent*)).ti,ab,kf.
16	or/10-15
17	9 and 16
18	Folic Acid/
19	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
20	or/18-19
21	17 and 20
22	letter/
23	editorial/
24	news/
25	exp historical article/
26	Anecdotes as Topic/
27	comment/
28	case report/
29	(letter or comment*).ti.
30	or/22-29
31	randomized controlled trial/ or random*.ti,ab.
32	30 not 31
33	animals/ not humans/
34	exp Animals, Laboratory/
35	exp Animal Experimentation/
36	exp Models, Animal/
37	exp Rodentia/
38	(rat or rats or mouse or mice or rodent*).ti.

#	Searches
39	or/32-38
40	21 not 39
41	limit 40 to English language
42	randomized controlled trial.pt.
43	controlled clinical trial.pt.
44	pragmatic clinical trial.pt.
45	randomi#ed.ab.
46	placebo.ab.
47	drug therapy.fs.
48	randomly.ab.
49	trial.ab.
50	groups.ab.
51	or/42-50
52	Clinical Trials as topic.sh.
53	trial.ti.
54	or/42-46,48,52-53
55	Meta-Analysis/
56	Meta-Analysis as Topic/
57	(meta analy* or metanaly* or metaanaly*).ti,ab.
58	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
59	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61	(search* adj4 literature).ab.
62	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
63	cochrane.jw.
64	or/55-63
65	41 and (54 or 64)
66	COMPARATIVE STUDIES/
67	FOLLOW-UP STUDIES/
68	TIME FACTORS/
69	chang$.tw.
70	evaluat$.tw.
71	reviewed.tw.
72	prospective$.tw.
73	retrospective$.tw.
74	baseline.tw.
75	cohort.tw.
76	case series.tw.
77	or/66-76
78	41 and 77
79	78 not 65
80	afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and

#	Searches
	the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/
81	"Organisation for Economic Co-Operation and Development"/
82	australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/
83	European Union/
84	Developed Countries/
85	or/81-84
86	80 not 85
87	65 not 86
88	79 not 86

Database: Embase

Date of last search: 04/12/2023

#	Searches
1	exp pregnancy/ or pregnant woman/ or prenatal care/ or prenatal period/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	prepregnancy care/
5	(periconception* or preconception* or pre conception* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	*body mass/ or *body size/ or *body weight/ or *body weight gain/ or *obesity/ or *abdominal obesity/ or *fat mass/ or *maternal obesity/ or *metabolically benign obesity/ or *morbid obesity/ or *normal weight obesity/ or *waist circumference/ or *waist hip ratio/ or *waist to height ratio/ or *weight height ratio/ or *skinfold thickness/ or *body fat distribution/
11	exp *adipose tissue/ or exp *obese patient/
12	(obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos* or (weight adj2 (manag* or gain* or increas* or excess or chang*))).ti,ab,kf.
13	(body mass index or BMI or quetelet index).ti,ab,kf.
14	(waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*).ti,ab,kf.
15	(skin fold* or skinfold* or body composition or (body fat adj3 percent*)).ti,ab,kf.
16	or/10-15
17	9 and 16
18	*folic acid/
19	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
20	or/18-19
21	17 and 20
22	letter.pt. or letter/
23	note.pt.
24	editorial.pt.
25	case report/ or case study/
26	(letter or comment*).ti.
27	or/22-26
28	randomized controlled trial/ or random*.ti,ab.
29	27 not 28

#	Searches
30	animal/ not human/
31	nonhuman/
32	exp Animal Experiment/
33	exp Experimental Animal/
34	animal model/
35	exp Rodent/
36	(rat or rats or mouse or mice or rodent*).ti.
37	or/29-36
38	21 not 37
39	limit 38 to English language
40	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
41	39 not 40
42	random*.ti,ab.
43	factorial*.ti,ab.
44	(crossover* or cross over*).ti,ab.
45	((doubl* or singl*) adj blind*).ti,ab.
46	(assign* or allocat* or volunteer* or placebo*).ti,ab.
47	crossover procedure/
48	single blind procedure/
49	randomized controlled trial/
50	double blind procedure/
51	or/42-50
52	systematic review/
53	meta-analysis/
54	(meta analy* or metanaly* or metaanaly*).ti,ab.
55	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
56	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
58	(search* adj4 literature).ab.
59	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
60	((pool* or combined) adj2 (data or trials or studies or results)).ab.
61	cochrane.jw.
62	or/52-61
63	41 and (51 or 62)
64	CONTROLLED STUDY/
65	TREATMENT OUTCOME/
66	MAJOR CLINICAL STUDY/
67	CLINICAL TRIAL/
68	evaluat$.tw.
69	reviewed.tw.
70	baseline.tw.
71	(compare$ or compara$).tw.
72	or/64-71
73	41 and 72
74	73 not 63
75	afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or

#	Searches
	kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/
76	"organisation for economic co-operation and development"/
77	exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or exp united kingdom/ or "turkey (republic)"/ or exp united states/ or western europe/
78	european union/
79	developed country/
80	or/76-79
81	75 not 80
82	63 not 81
83	74 not 81

Database: Cochrane Database of Systematic Reviews, Issue 12 of 12, December 2023 & Cochrane Central Register of Controlled Trials, Issue 12 of 12, December 2023

Date of last search: 04/12/2023

#	Searches
#1	MeSH descriptor: [Pregnancy] explode all trees
#2	MeSH descriptor: [Pregnant Women] this term only
#3	MeSH descriptor: [Prenatal Care] this term only
#4	(antenatal* or ante NEXT natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre NEXT natal*):ti,ab,kw
#5	{OR #1-#4}
#6	MeSH descriptor: [Preconception Care] this term only
#7	(periconcept* or peri NEXT concept* or preconcept* or pre NEXT concept* or prepregnan* or pre NEXT pregnan*):ti,ab,kw
#8	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) NEAR/3 (baby or babies or conceiving or pregnan* or conception* or conceive*)):ti,ab,kw
#9	(start* near/2 family):ti,ab,kw
#10	{OR #6-#9}
#11	#5 or #10
#12	MeSH descriptor: [Adiposity] this term only
#13	MeSH descriptor: [Body Mass Index] this term only
#14	MeSH descriptor: [Body Size] this term only
#15	MeSH descriptor: [Body Weight] this term only
#16	MeSH descriptor: [Overweight] this term only
#17	MeSH descriptor: [Obesity] this term only
#18	MeSH descriptor: [Obesity, Abdominal] this term only
#19	MeSH descriptor: [Obesity, Maternal] this term only
#20	MeSH descriptor: [Obesity, Metabolically Benign] this term only
#21	MeSH descriptor: [Obesity, Morbid] this term only
#22	MeSH descriptor: [Waist Circumference] this term only
#23	MeSH descriptor: [Waist-Hip Ratio] this term only
#24	MeSH descriptor: [Waist-Height Ratio] this term only

#	Searches
#25	MeSH descriptor: [Weight Gain] this term only
#26	MeSH descriptor: [Skinfold Thickness] this term only
#27	MeSH descriptor: [Body Fat Distribution] this term only
#28	MeSH descriptor: [Adipose Tissue] explode all trees
#29	(obes* or overweight or "over weight" or corpulen* or heavy or heavier or fat or adipos* or (weight NEAR/2 (manag* or gain* or increas* or excess or chang*))):ti,ab,kw
#30	("body mass index" or BMI or "quetelet index"):ti,ab,kw
#31	(waist NEXT circumference* or waist NEXT hip NEXT ratio* or waist NEXT height NEXT ratio* or weight NEXT height NEXT ratio*):ti,ab,kw
#32	(skin NEXT fold* or skinfold* or "body composition" or (body NEXT fat NEAR/3 percent*)):ti,ab,kw
#33	{OR #12-#32}
#34	#11 AND #33
#35	MeSH descriptor: [Folic Acid] this term only
#36	(folic NEXT acid* or folate* or folacin or "vitamin b9" or "vitamin b 9" or "vitamin m" or pteroylglutamic NEXT acid* or folvite):ti,ab,kw
#37	#35 or #36
#38	#34 and #37
#39	conference:pt or (clinicaltrials or trialsearch):so
#40	#38 not #39

Database: Epistemonikos

Date of last search: 04/12/2023

#	Searches
1	(title:(pregnan* OR prenatal OR periconcept* OR preconcept* OR prepregnan*) OR abstract:(pregnan* OR prenatal OR periconcept* OR preconcept* OR prepregnan*))
2	(title:(obese OR overweight OR adipos*) OR abstract:(obese OR overweight OR adipos*))
3	1 and 2
4	(title:((folic acid* OR folate* OR folacin OR vitamin b9 OR vitamin b 9 OR vitamin m OR pteroylglutamic acid* OR folvite)) OR abstract:((folic acid* OR folate* OR folacin OR vitamin b9 OR vitamin b 9 OR vitamin m OR pteroylglutamic acid* OR folvite)))
5	3 and 5 [Filters: protocol=no]

Economic searches

Database: Medline

Date of last search: 04/12/2023

#	Searches
1	exp Pregnancy/ or Pregnant Women/ or Prenatal Care/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	Preconception Care/
5	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	adiposity/ or body mass index/ or body size/ or body weight/ or overweight/ or obesity/ or obesity, abdominal/ or obesity, maternal/ or obesity, metabolically benign/ or obesity, morbid/ or waist circumference/ or waist-hip ratio/ or waist-height ratio/ or weight gain/ or skinfold thickness/ or body fat distribution/
11	exp Adipose Tissue/
12	(obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos* or (weight adj2 (manag* or gain* or increas* or excess or chang*))).ti,ab,kf.

#	Searches
13	(body mass index or BMI or quetelet index).ti,ab,kf.
14	(waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*).ti,ab,kf.
15	(skin fold* or skinfold* or body composition or (body fat adj3 percent*)).ti,ab,kf.
16	or/10-15
17	9 and 16
18	Folic Acid/
19	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
20	or/18-19
21	17 and 20
22	letter/
23	editorial/
24	news/
25	exp historical article/
26	Anecdotes as Topic/
27	comment/
28	case reports/
29	(letter or comment*).ti.
30	or/22-29
31	randomized controlled trial/ or random*.ti,ab.
32	30 not 31
33	animals/ not humans/
34	exp Animals, Laboratory/
35	exp Animal Experimentation/
36	exp Models, Animal/
37	exp Rodentia/
38	(rat or rats or mouse or mice or rodent*).ti.
39	or/32-38
40	21 not 39
41	limit 40 to English language
42	Economics/
43	Value of life/
44	exp "Costs and Cost Analysis"/
45	exp Economics, Hospital/
46	exp Economics, Medical/
47	exp Resource Allocation/
48	Economics, Nursing/
49	Economics, Pharmaceutical/
50	exp "Fees and Charges"/
51	exp Budgets/
52	budget*.ti,ab.
53	cost*.ti,ab.
54	(economic* or pharmaco?economic*).ti,ab.
55	(price* or pricing*).ti,ab.
56	(financ* or fee or fees or expenditure* or saving*).ti,ab.
57	(value adj2 (money or monetary)).ti,ab.
58	resourc* allocat*.ti,ab.
59	(fund or funds or funding* or funded).ti,ab.
60	(ration or rations or rationing* or rationed).ti,ab.
61	ec.fs.
62	or/42-61
63	exp models, economic/
64	*Models, Theoretical/

#	Searches
65	*Models, Organizational/
66	markov chains/
67	monte carlo method/
68	exp Decision Theory/
69	(markov* or monte carlo).ti,ab.
70	econom* model*.ti,ab.
71	(decision* adj2 (tree* or analy* or model*)).ti,ab.
72	or/63-71
73	quality-adjusted life years/
74	sickness impact profile/
75	(quality adj2 (wellbeing or well being)).ti,ab.
76	sickness impact profile.ti,ab.
77	disability adjusted life.ti,ab.
78	(qal* or qtime* or qwb* or daly*).ti,ab.
79	(euroqol* or eq5d* or eq 5*).ti,ab.
80	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
81	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
82	(hui or hui1 or hui2 or hui3).ti,ab.
83	(health* year* equivalent* or hye or hyes).ti,ab.
84	discrete choice*.ti,ab.
85	rosser.ti,ab.
86	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
87	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
88	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
89	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
90	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
91	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
92	or/73-91
93	41 and (62 or 72 or 92)

Database: Embase

Date of last search: 04/12/2023

#	Searches
1	exp pregnancy/ or pregnant woman/ or prenatal care/ or prenatal period/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	prepregnancy care/
5	(periconception* or preconception* or pre conception* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	*body mass/ or *body size/ or *body weight/ or *body weight gain/ or *obesity/ or *abdominal obesity/ or *fat mass/ or *maternal obesity/ or *metabolically benign obesity/ or *morbid obesity/ or *normal weight obesity/ or *waist circumference/ or *waist hip ratio/ or *waist to height ratio/ or *weight height ratio/ or *skinfold thickness/ or *body fat distribution/
11	exp *adipose tissue/ or exp *obese patient/
12	(obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos* or (weight adj2 (manag* or gain* or increas* or excess or chang*))).ti,ab,kf.
13	(body mass index or BMI or quetelet index).ti,ab,kf.
14	(waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*).ti,ab,kf.
15	(skin fold* or skinfold* or body composition or (body fat adj3 percent*)).ti,ab,kf.

#	Searches
16	or/10-15
17	9 and 16
18	*folic acid/
19	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
20	or/18-19
21	17 and 20
22	letter.pt. or letter/
23	note.pt.
24	editorial.pt.
25	case report/ or case study/
26	(letter or comment*).ti.
27	or/22-26
28	randomized controlled trial/ or random*.ti,ab.
29	27 not 28
30	animal/ not human/
31	nonhuman/
32	exp Animal Experiment/
33	exp Experimental Animal/
34	animal model/
35	exp Rodent/
36	(rat or rats or mouse or mice or rodent*).ti.
37	or/29-36
38	21 not 37
39	limit 38 to English language
40	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
41	39 not 40
42	health economics/
43	exp economic evaluation/
44	exp health care cost/
45	exp fee/
46	budget/
47	funding/
48	resource allocation/
49	budget*.ti,ab.
50	cost*.ti,ab.
51	(economic* or pharmaco?economic*).ti,ab.
52	(price* or pricing*).ti,ab.
53	(financ* or fee or fees or expenditure* or saving*).ti,ab.
54	(value adj2 (money or monetary)).ti,ab.
55	resourc* allocat*.ti,ab.
56	(fund or funds or funding* or funded).ti,ab.
57	(ration or rations or rationing* or rationed).ti,ab.
58	or/42-57
59	statistical model/
60	exp economic aspect/
61	59 and 60
62	*theoretical model/
63	*nonbiological model/
64	stochastic model/
65	decision theory/
66	decision tree/
67	monte carlo method/

#	Searches
68	(markov* or monte carlo).ti,ab.
69	econom* model*.ti,ab.
70	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71	or/61-70
72	quality adjusted life year/
73	"quality of life index"/
74	short form 12/ or short form 20/ or short form 36/ or short form 8/
75	sickness impact profile/
76	(quality adj2 (wellbeing or well being)).ti,ab.
77	sickness impact profile.ti,ab.
78	disability adjusted life.ti,ab.
79	(qal* or qtime* or qwb* or daly*).ti,ab.
80	(qal* or qtime* or qwb* or daly*).ti,ab.
81	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
82	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
83	(hui or hui1 or hui2 or hui3).ti,ab.
84	(health* year* equivalent* or hye or hyes).ti,ab.
85	discrete choice*.ti,ab.
86	rosser.ti,ab.
87	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
88	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
89	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
90	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
91	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
92	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
93	or/72-92
94	41 and (58 or 71 or 93)

Database: INAHTA HTA

Date of last search: 04/12/2023

#	Searches
1	"Pregnancy"[mhe]
2	"Pregnant Women"[mh]
3	"Prenatal Care"[mh]
4	((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))[Title] OR ((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))[abs]
5	or/1-4
6	"Preconception Care"[mh]
7	((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))[Title] OR ((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))[abs]
8	(((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) and (baby or babies or conceiving or pregnan* or conception* or conceive*)))[Title] OR (((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) and (baby or babies or conceiving or pregnan* or conception* or conceive*)))[abs]
9	((start* and family))[Title] OR ((start* and family))[abs]
10	or/6-9
11	5 or 10
12	"Adiposity"[mh]
13	"Body Mass Index"[mh]
14	"Body Size"[mh]
15	"Body Weight"[mh]
16	"Overweight"[mh]
17	"Obesity"[mh]

#	Searches
18	"Obesity Abdominal"[mh]
19	"Obesity Maternal"[mh]
20	"Obesity Metabolically Benign"[mh]
21	"Obesity Morbid"[mh]
22	"Waist Circumference"[mh]
23	"Waist-Hip Ratio"[mh]
24	"Waist-Height Ratio"[mh]
25	"Weight Gain"[mh]
26	"Skinfold Thickness"[mh]
27	"Body Fat Distribution"[mh]
28	"Adipose Tissue"[mhe]
29	((obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos*))[Title] OR ((obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos*))[abs]
30	((weight and (manag* or gain* or increas* or excess or chang*)))[Title] OR ((weight and (manag* or gain* or increas* or excess or chang*)))[abs]
31	((body mass index or BMI or quetelet index))[Title] OR ((body mass index or BMI or quetelet index))[abs]
32	((waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*))[Title] OR ((waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*))[abs]
33	((skin fold* or skinfold* or body composition))[Title] OR ((skin fold* or skinfold* or body composition))[abs]
34	((body fat and percent*)))[Title] OR ((body fat and percent*)))[abs]
35	Or/12-34
36	11 and 35
37	"Folic Acid"[mh]
38	((folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite))[Title] OR ((folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite))[abs]
39	Or/37-38
40	36 and 39

Database: CRD HTA (last updated October 2016)

Date of last search: 19/05/2022

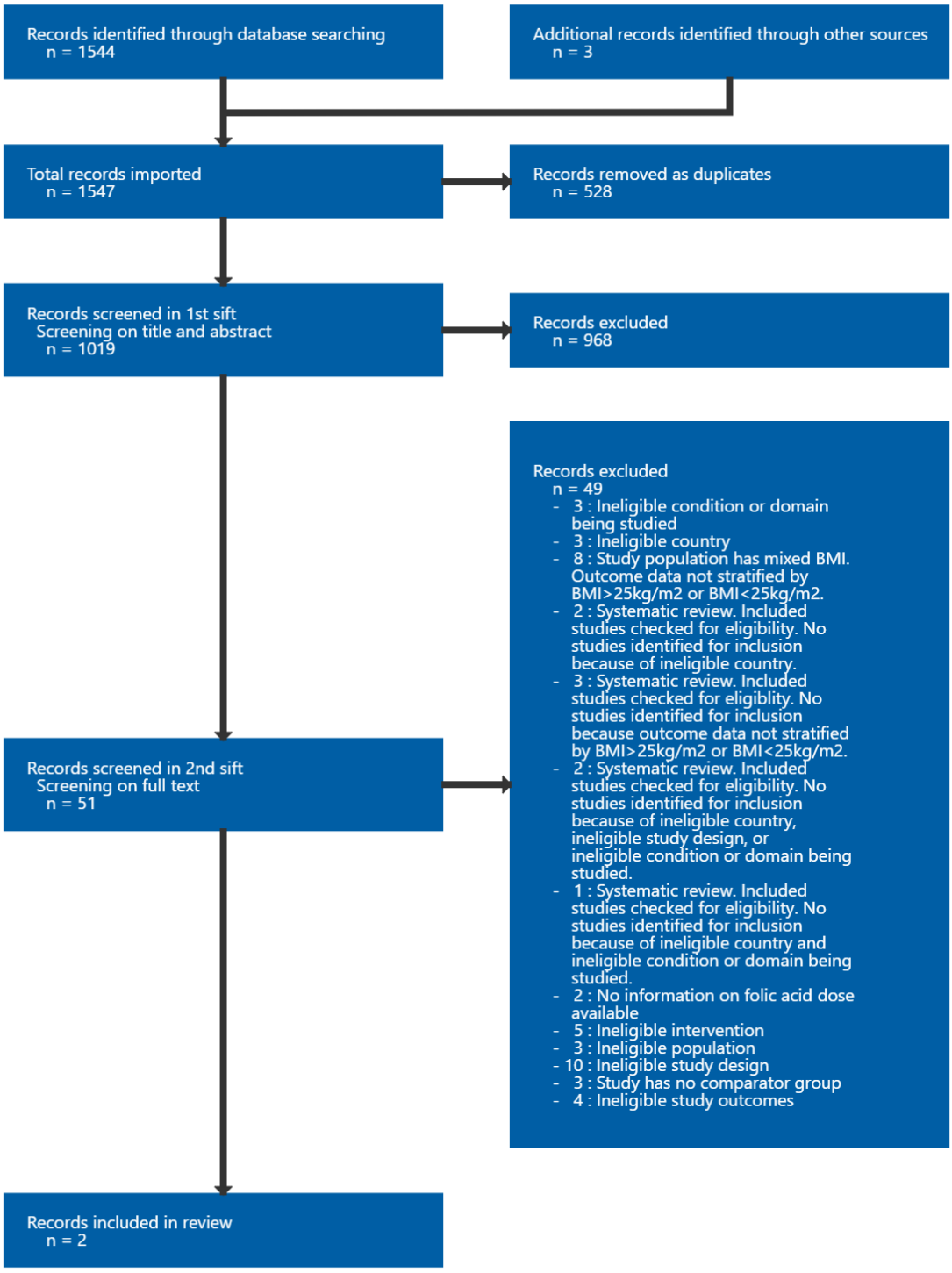
#	Searches
1	MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES IN HTA
2	MeSH DESCRIPTOR Pregnant Women IN HTA
3	MeSH DESCRIPTOR Prenatal Care EXPLODE ALL TREES IN HTA
4	(((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))) and (Full publication record:ZDT) IN HTA
5	MeSH DESCRIPTOR Preconception Care IN HTA
6	(((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
7	((((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) NEAR3 (baby or babies or conceiving or pregnan* or conception* or conceive*)))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
8	(((start* NEAR2 family))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
9	#1 OR #2 OR #3 OR #4
10	#5 OR #6 OR #7 OR #8
11	#9 OR #10
12	MeSH DESCRIPTOR Adiposity IN HTA
13	MeSH DESCRIPTOR Body Mass Index IN HTA
14	MeSH DESCRIPTOR Body Size IN HTA
15	MeSH DESCRIPTOR Body Weight IN HTA
16	MeSH DESCRIPTOR Overweight IN HTA
17	MeSH DESCRIPTOR Obesity IN HTA
18	MeSH DESCRIPTOR Obesity, Abdominal IN HTA
19	MeSH DESCRIPTOR Obesity, Maternal IN HTA

#	Searches
20	MeSH DESCRIPTOR Obesity, Metabolically Benign IN HTA
21	MeSH DESCRIPTOR Obesity, Morbid IN HTA
22	MeSH DESCRIPTOR Waist Circumference IN HTA
23	MeSH DESCRIPTOR Waist-Hip Ratio IN HTA
24	MeSH DESCRIPTOR Waist-Height Ratio IN HTA
25	MeSH DESCRIPTOR Weight Gain IN HTA
26	MeSH DESCRIPTOR Skinfold Thickness IN HTA
27	MeSH DESCRIPTOR Body Fat Distribution IN HTA
28	MeSH DESCRIPTOR Adipose Tissue EXPLODE ALL TREES IN HTA
29	(((obes* or overweight or over weight or corpulen* or heavy or heavier or fat or adipos*))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
30	(((weight NEAR2 (manag* or gain* or increas* or excess or chang*)))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
31	(((body mass index or BMI or quetelet index))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
32	(((waist circumference* or waist hip ratio* or waist height ratio* or weight height ratio*))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
33	(((skin fold* or skinfold* or body composition))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
34	(((body fat NEAR3 percent*))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
35	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
36	#11 AND #35
37	MeSH DESCRIPTOR Folic Acid IN HTA
38	(((folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
39	#37 OR #38
40	#36 AND #39

Appendix C Effectiveness evidence study selection

Study selection for: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Figure 1: Effectiveness evidence study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Table 4: Evidence tables

Catov, 2009

Bibliographic Reference	Catov, J. M.; Nohr, E. A.; Bodnar, L. M.; Knudson, V. K.; Olsen, S. F.; Olsen, J.; Association of periconceptional multivitamin use with reduced risk of preeclampsia among normal-weight women in the Danish National Birth Cohort; American Journal of Epidemiology; 2009; vol. 169 (no. 11); 1304-11

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	1997 to 2003
Inclusion criteria	Not reported
Exclusion criteria	• Unknown recruitment date or joined study at <5 weeks' gestation or >24 weeks' gestation; • Single supplement use (other than folate); • No report of weeks of supplement use; • Women with non- livebirths, multi fetal gestations, or pre-existing diabetes.
Patient characteristics	**Maternal age, years, n (%);** mean (SD) - NR 200µg folic acid (in multivitamin supplementation): <21: 148 (0.8)

	21–25: 2337 (12.6) 26–30: 8481 (45.7) 31–35: 5686 (30.7) ≥36: 1899 (10.2) No intervention: <21: 199 (2.6) 21–25 1251 (16.5) 26–30 3021 (39.8) 31–35 2241 (29.6) ≥36 870 (11.5) **Multiparous, n (%)** 200µg folic acid (in multivitamin supplementation): 8719 (47.0) No intervention: 4299 (57.7) **Maternal BMI, kg/m^2, n (%);** mean (SD) - NR 200µg folic acid (in multivitamin supplementation): <18.5: 801 (4.3) 18.5 - 24.9: 12621 (68.0) 25 - 29.9: 3544 (19.1) ≥30: 1585 (8.6) No intervention: <18.5: 324 (4.3)

	18.5 - 24.9: 4734 (62.4) 25 - 29.9: 1677 (22.1) ≥30: 847 (11.2) **Gestational age at recruitment in weeks, mean (SD)** 200µg folic acid (in multivitamin supplementation): 10.9 (3.5) No intervention: 11.2 (3.8) **Low socio occupational status, n (%)** 200µg folic acid (in multivitamin supplementation): 596 (3.2) No intervention: 517 (6.8)
Intervention(s)/control	Intervention: 200µg folic acid (in multivitamin supplementation)* Control: no intervention (non-users) Nonusers were women with a body mass index of 22 kg/ m^2, the median body mass index for the entire study population, were the referent. *no outcome data stratified by BMI available for women who took folate only supplements
Duration of follow-up	From gestational day 140 to the date of delivery
Sources of funding	Not industry funded

Sample size	N=28601* women n=18551 200µg folic acid (in multivitamin supplementation) n=7582 no intervention *includes no intervention, 200µg folic acid (in multivitamin supplementation), and folate only users
Other information	Contents of most commonly used multivitamin supplement: Vitamin A, Thiamin (B1), Riboflavin (B12), Vitamin B6, Vitamin B12, Folic acid, Niacin, Pantothenic acid, Vitamin C, Vitamin D, Vitamin E, Iron, Zinc, Copper, Iodine, Manganese, Chromium, Selenium, Molybdenum. Regular folic acid users were defined as those who used multivitamins during the 12 week periconceptional period. OR adjusted for the following covariates: smoking, parity, chronic hypertension and gestational age at recruitment

BMI: body mass index; µg: microgram; n: number of participants; NR: not reported; SD: standard deviation

Study arms

No intervention (n = 7582)

200µg folic acid (in multivitamin supplementation) (n = 18551)

Outcomes

Outcome	**No intervention n = 7582 (BMI 22 kg/m^2)**	**200µg folic acid (in multivitamin supplementation), n = 18551**
Risk of preeclampsia (BMI 26kg/m^2) Hazard Ratio* (95% CI)	referent	1.16 (0.93 to 1.44)
Risk of preeclampsia (BMI 28kg/m^2) Hazard Ratio* (95% CI)	referent	1.41 (1.13 to 1.77)

Outcome	No intervention n = 7582 (BMI 22 kg/m^2)	200µg folic acid (in multivitamin supplementation), n = 18551
Risk of preeclampsia (BMI 30kg/m^2) Hazard Ratio* (95% CI)	referent	1.73 (1.36 to 2.18)

**Model adjusted for smoking, parity, chronic hypertension, and gestational age at recruitment.*
BMI: body mass index; CI: confidence interval

Preeclampsia defined according to ICD10, codes O14–O15 (gestational hypertension after 20 weeks' gestation (blood pressure, >140/90 mm Hg) that resolves postpartum, in combination with proteinuria of >=0.3 g/L)

Critical appraisal - NGA Critical appraisal – ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(It is unclear whether there are any significant differences between groups at baseline. For both groups, folic acid dose is lower than the UK daily standard)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(No serious bias in the selection of participants)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups were clearly defined a priori.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(The intervention group used reported use of lots of vitamins but the control group did not. Participants followed their intended interventions.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Not all outcome data available for all who enrolled.)*

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Folic acid/multivitamin intake was patient reported)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data is reported appropriately.)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Partially Applicable

NGA: National Guideline Alliance; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions; UK: United Kingdom

Martinussen, 2015

Bibliographic Reference	Martinussen, M. P.; Bracken, M. B.; Triche, E. W.; Jacobsen, G. W.; Risnes, K. R.; Folic acid supplementation in early pregnancy and the risk of preeclampsia, small for gestational age offspring and preterm delivery; European Journal of Obstetrics, Gynecology, & Reproductive Biology; 2015; vol. 195; 94-9

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	1996-2000
Inclusion criteria	• Pregnancy was before 24 weeks' gestational age at enrolment; • Did not have insulin-dependent diabetes mellitus;

	• Spoke English or Spanish; • Did not intend to terminate their pregnancy.
Exclusion criteria	Not reported
Patient characteristics	Significant differences at baseline between groups were identified for: maternal age (=>35 years), maternal married status (divorced), maternal ethnicity (other), maternal education (>16 years), smoking in pregnancy (smoked throughout pregnancy), parity (>=3), previous stillbirths or miscarriages (no). **Maternal age in years** (n = 3645), **n (%);** mean (SD) - NR <20: 424 (11.6) 20≤25: 897 (24.6) 25≤30: 1117 (30.6) 30≤35: 906 (24.9) ≥35: 302 (8.3) **Preeclampsia, n (%)** Yes: 128 (4.5) No: 3519 (96.5) **BMI, kg/m^2, n (%);** mean (SD) - NR <25: 2431 (68.3) ≥25: 1128 (31.7) **Parity, n (%)** 0: 1514 (41.5) 1: 1347 (37.0)

	2: 561 (15.4) ≥3: 222 (6.1) **Maternal education (n = 3643), n (%)** <12 years: 851 (33.3) 12 years: 1213 (33.1) 13–16 years: 1205 (10.3) >16 years: 375 (NR) **Maternal ethnicity** (n = 3641), **n (%)** White: 2505 (68.8) African American: 290 (8.0) Hispanic: 700 (19.2) Asian: 67 (1.8) Other: 79 (2.2)
Intervention(s)/control	**Intervention** Folic acid use (on average from the month before pregnancy until the third month of pregnancy)- >200 µg /day. Mean folic acid intake in first trimester was defined as the average intake over these four months. For each month and for the first trimester overall, daily folic acid intake was divided into a dichotomous variable of use (no use: <200mcg daily and use: >200µg average use). **Control** Folic acid use (on average from the month before pregnancy until the third month of pregnancy)- <200 µg /day

Duration of follow-up	Followed from the first trimester of pregnancy to birth.
Sources of funding	Not industry funded.
Sample size	N=3647* women *some baseline data missing for some participants
Other information	OR adjusted for the following covariates: study asthma in pregnancy or nutrition in pregnancy maternal age, maternal ethnicity, maternal education, maternal marital status, maternal smoking in pregnancy and any miscarriages or stillbirths in previous pregnancies Strata: BMI ≥25kg/m^2

AIP: Asthma in Pregnancy Study; BMI: body mass index; µg: microgram; n: number of participants; NIP: Nutrition in Pregnancy Study; OR: odds ratio

Study arms

No intervention (n = 346)

Use of folic acid supplements (n = 3301)

Outcomes

Outcome	No intervention, n = 346	Use of folic acid supplements, n = 3301
BMI >=25 kg/m^2 (folic acid started one month before conception) n=1128 Odds Ratio* (95% CI)	referent	1.0 (0.5 to 2.0)
BMI >=25kg/m^2 (folic acid taken throughout first trimester) n=1128 Odds Ratio* (95% CI)	referent	1.4 (0.5 to 3.5)

**Adjusted for: study (AIP or NIP), maternal age, maternal ethnicity, maternal education, maternal marital status, maternal smoking in pregnancy and any miscarriages or stillbirths in previous pregnancies.*
BMI: body mass index; CI: confidence interval; n: number of participants

"Preeclampsia defined as meeting both of the following criteria: 1) de novo hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic on two or more occasions at least 6 h apart beginning after the 20th week of gestation; and 2) accompanying proteinuria, defined as urinary protein concentrations of 30 mg/dl or greater (equivalent to a dipstick value of 1+ from two or more specimens collected at least 4 h apart, or one or more urinary dipstick values of 2+ near the end of pregnancy, or one or more catheterized dipstick values of 1+ during delivery hospitalization, or 24-h urine collection with protein of ≥300 mg."

Critical appraisal - NGA Critical appraisal – ROBINS-I checklist

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(Some significant baseline differences but outcomes have been adjusted for confounders so low risk.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(No serious bias in the selection of participants)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups clearly defined a priori)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Participants followed their intended interventions.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Some outcome data missing but low risk of bias due to missing data.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Folic acid intake was participant reported. Outcome measure not influenced by knowledge of intervention.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data reported appropriately)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	N/A

Section	Question	Answer
Overall bias	Directness	Partially Applicable

N/A: not applicable; NGA: National Guideline Alliance; ROBIS: Risk of Bias in Systematic Reviews.

Appendix E Forest plots

Forest plots for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Table 5: Evidence profile for comparison between folic acid supplementation 200µg (in multivitamin supplementation) and no intervention (no multivitamin and folic acid supplementation) in women with BMI >25kg/m^2 in singleton pregnancies who took folic acid supplementation during the periconceptional period

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Folic acid supplementation200µg (in multivitamin supplementation)	No intervention	Relative (95% CI)	Absolute		
Preeclampsia - BMI 26kg/m^2 (referent: BMI 22 with no multivitamin and folic acid supplementation) (follow-up - gestational day 140 to date of delivery)												
1 Catov 2009	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7582	18551	aHR* 1.16 (0.93 to 1.45)	-	LOW **NO IMP. DIFF.**	CRITICAL
Preeclampsia - BMI 28 kg/m^2 (referent: BMI 22 with no multivitamin and folic acid supplementation) (follow-up - gestational day 140 to date of delivery)												
1 Catov 2009	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7582	18551	aHR* 1.41 (1.13 to 1.76)	-	LOW **IMP. HARM**	CRITICAL
Preeclampsia - BMI 30 kg/m^2 (referent: BMI 22 with no multivitamin and folic supplementation) (follow-up - gestational day 140 to date of delivery)												
1 Catov 2009	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7582	18551	aHR* 1.73 (1.36 to 2.20)	-	MODERATE **IMP. HARM**	CRITICAL

**Model adjusted for smoking, parity, chronic hypertension, and gestational age at recruitment.*
[1] Moderate risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[2] Statistical significance used to assess clinical importance. Number of events in intervention and control arm not reported in the paper. Hence default values used to assess imprecision, 95% CI crosses 1 MID (0.8 and 1.25)

Table 6: Evidence profile for comparison between folic acid supplementation >200µg and folic acid supplementation <200µg in women with BMI ≥25kg/m^2 in singleton pregnancies who took folic acid supplementation during the periconceptional period and during the first three months of pregnancy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Folic acid supplementation >200µg	Folic acid supplementation <200µg	Relative (95% CI)	Absolute		
Preeclampsia (folic acid use started one month before conception) - follow-up first trimester of pregnancy to birth												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Folic acid supplementation >200µg	Folic acid supplementation <200µg	Relative (95% CI)	Absolute		
1 Martinussen 2015	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	346	3301	aOR* 1.00 (0.50 to 2.00)	-	VERY LOW **NO IMP. DIFF.**	CRITICAL
Preeclampsia (folic acid use throughout the first trimester) - follow-up first trimester of pregnancy to birth												
1 Martinussen 2015	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	346	3301	aOR* 1.40 (0.50 to 3.92)	-	VERY LOW **NO IMP. DIFF.**	CRITICAL

**Model adjusted for asthma in pregnancy, nutrition in pregnancy, maternal age, maternal ethnicity, maternal education, maternal marital status, maternal smoking in pregnancy and any miscarriages or stillbirths in previous pregnancies.*

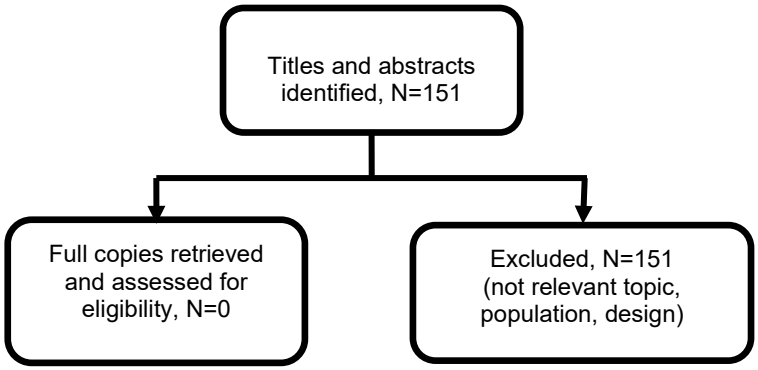
[1] Moderate risk of bias in the evidence contributing to the outcomes as per ROBINS-I

[2] Statistical significance used to assess clinical importance. Number of events in intervention and control arm not reported in the paper. Hence default values used to assess imprecision 95% CI crosses 2 MIDs (0.8 and 1.25)

Appendix G Economic evidence study selection

Study selection for: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Figure 2. Flow diagram of selection process for economic evaluations



Appendix H Economic evidence tables

Economic evidence tables for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

Excluded effectiveness studies

Table 7: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Blot, I.; Rey, A.; Kaltwasser, J. P. (1982) Folate and iron deficiencies in mothers and their newborn children. Blut 44(5): 297-303	- Ineligible intervention *Study assesses iron and folate status with ferritinemia. There is no comparison of different doses of folic acid.*
Bodnar LM, Tang G, Ness RB et al. (2006) Periconceptional multivitamin use reduces the risk of preeclampsia. American Journal of Epidemiology 164(5): 470-477	- No information on folic acid dose available
Case, A. P., Ramadhani, T. A., Canfield, M. A. et al. (2007) Folic acid supplementation among diabetic, overweight, or obese women of childbearing age. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing 36(4): 335-41	- Study has no comparator group
Catov, J. M., Bodnar, L. M., Ness, R. B. et al. (2007) Association of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births. American Journal of Epidemiology 166(3): 296-303	- Ineligible condition or domain being studied *Study assesses the relation between periconceptional multivitamin use and the risk of small-for-gestational-age*
Ciulei, Mihaela A, Smith, Emily R, Perumal, Nandita et al. (2023) Nutritious Supplemental Foods for Pregnant Women from Food Insecure Settings: Types, Nutritional Composition, and Relationships to Health Outcomes. Current developments in nutrition 7(6): 100094	- Ineligible study design *Narrative review. Screened for relevant references.*
Czeizel, A. E.; Métneki, J.; Dudás, I. (1994) The higher rate of multiple births after periconceptional multivitamin supplementation: an analysis of causes. Acta geneticae medicae et gemellologiae 43(34): 175-184	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
da Silva, V. R., Hausman, D. B., Kauwell, G. P. et al. (2013) Obesity affects short-term folate pharmacokinetics in women of childbearing age. International Journal of Obesity 37(12): 1608-10	- Ineligible intervention

Study	Code [Reason]
	Study compares the relationship between BMI and the short-term pharmacokinetic response to folic acid
Daly, M., Kipping, R. R., Tinner, L. E. et al. (2022) Preconception exposures and adverse pregnancy, birth and postpartum outcomes: Umbrella review of systematic reviews. Paediatric and Perinatal Epidemiology 36(2): 288-299	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Devakumar, D., Fall, C. H., Sachdev, H. S. et al. (2016) Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis. BMC Medicine 14: 90	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because of ineligible country. *All studies conducted in countries other than high income countries (as defined by the OECD)*
Donovan, S., Dewey, K., Novotny, R. et al. (2020) What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and health outcomes?. USDA Nutrition Evidence Systematic Review. USDA Nutrition Evidence Systematic Reviews 07: 07	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Duncan, K., Erickson, A. C., Egeland, G. M. et al. (2018) Red blood cell folate levels in Canadian Inuit women of childbearing years: influence of food security, body mass index, smoking, education, and vitamin use. Canadian Journal of Public Health. Revue Canadienne de Sante Publique 109(56): 684-691	- Ineligible intervention *Study assesses whether red blood cell folate levels reach target levels when access to folate-rich foods limited and vitamin use is low*
Farah, N., Kennedy, C., Turner, C. et al. (2013) Maternal obesity and pre-pregnancy folic acid supplementation. Obesity Facts 6(2): 211-5	- Study has no comparator group
Fraticelli, F., Celentano, C., Zecca, I. A. et al. (2018) Effect of inositol stereoisomers at different dosages in gestational diabetes: an open-label, parallel, randomized controlled trial. Acta Diabetologica 55(8): 805-812	- Ineligible condition or domain being studied *Study assesses the effect of different dosages of inositol stereoisomers supplementation on insulin resistance levels and several maternal-fetal outcomes in gestational diabetes mellitus in women*
Furness, D. L., Yasin, N., Dekker, G. A. et al. (2012) Maternal red blood cell folate concentration at 10-12 weeks gestation and pregnancy outcome. Journal of Maternal-Fetal & Neonatal Medicine 25(8): 1423-7	- Ineligible study design *Retrospective case control study*

Study	Code [Reason]
Gomber, S., Agarwal, K. N., Mahajan, C. et al. (2002) Impact of daily versus weekly hematinic supplementation on anemia in pregnant women. Indian Pediatrics 39(4): 339-46	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in India.*
Haider, B. A.; Yakoob, M. Y.; Bhutta, Z. A. (2011) Effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes. BMC Public Health 11suppl3: 19	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because of ineligible country. *All studies conducted in countries other than high income countries (as defined by the OECD)*
Hininger, I., Favier, M., Arnaud, J. et al. (2004) Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometrics measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. European journal of clinical nutrition 58(1): 52-59	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Jankovic-Karasoulos, Tanja, Smith, Melanie D, Leemaqz, Shalem et al. (2023) Elevated Maternal Folate Status and Changes in Maternal Prolactin, Placental Lactogen and Placental Growth Hormone Following Folic Acid Food Fortification: Evidence from Two Prospective Pregnancy Cohorts. Nutrients 15(7)	- Ineligible intervention *Study aimed to establish whether maternal one-carbon metabolism and hormones that regulate glucose homeostasis change in healthy pregnancies post-folic acid food fortification.*
Kirke P; Daly L; Elwood J (1992) A randomised trial of low dose folic acid to prevent neural tube defects. The Irish Vitamin Study Group. Archives of Disease in Childhood: 1442-1446	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Krapels, I. P., van Rooij, I. A., Ocke, M. C. et al. (2004) Maternal nutritional status and the risk for orofacial cleft offspring in humans. Journal of Nutrition 134(11): 3106-13	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Lassi, Z. S., Salam, R. A., Haider, B. A. et al. (2013) Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. Cochrane Database of Systematic Reviews	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Ma, C., Carmichael, S. L., Scheuerle, A. E. et al. (2010) Association of microtia with maternal obesity and periconceptional folic acid use. American Journal of Medical Genetics, Part A 152(11): 2756-2761	- Ineligible condition or domain being studied *Study examines the association of microtia with intake of folic-acid supplements and obesity*

Study	Code [Reason]
Maffoni, S., De Giuseppe, R., Stanford, F. C. et al. (2017) Folate status in women of childbearing age with obesity: a review. Nutrition Research Reviews 30(2): 265-271	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because of ineligible country, ineligible study design, or ineligible condition or domain being studied.
Manandhar, M.; Beydoun, H.; Kancherla, V. (2020) Association between body mass index and folate insufficiency indicative of neural tube defects risk among nonpregnant women of childbearing age in the United States, NHANES, 2007-2010. Birth Defects Research 112(6): 490-502	- Study has no comparator group
McMahon, D. M., Liu, J., Zhang, H. et al. (2013) Maternal obesity, folate intake, and neural tube defects in offspring. Birth Defects Research Part A - Clinical and Molecular Teratology 97(2): 115-122	- Ineligible study design *Case-control study*
Morse, N. L. (2012) Benefits of docosahexaenoic acid, folic acid, vitamin D and iodine on foetal and infant brain development and function following maternal supplementation during pregnancy and lactation. Nutrients 4(7): 799-840	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Obeid, R.; Holzgreve, W.; Pietrzik, K. (2019) Folate supplementation for prevention of congenital heart defects and low birth weight: an update. Cardiovascular Diagnosis & Therapy 9(suppl2): S424-S433	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Parker, S. E., Yazdy, M. M., Tinker, S. C. et al. (2013) The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida. American Journal of Obstetrics and Gynecology 209(3): 239.e1-239.e8	- Ineligible study design *Case-control study*
Patti, Marisa A, Braun, Joseph M, Arbuckle, Tye E et al. (2022) Associations between folic acid supplement use and folate status biomarkers in the first and third trimesters of pregnancy in the Maternal-Infant Research on Environmental Chemicals (MIREC) Pregnancy Cohort Study. The American journal of clinical nutrition 116(6): 1852-1863	- Ineligible population *63% of the population had BMI<25.*
Petersen, J. M., Parker, S. E., Benedum, C. M. et al. (2019) Periconceptional folic acid and risk for neural tube defects among higher risk	- Ineligible study design *Case-control study*

Study	Code [Reason]
pregnancies. Birth Defects Research 111(19): 1501-1512	
Petry, C. J., Ong, K. K., Hughes, I. A. et al. (2021) Folic acid supplementation during pregnancy and associations with offspring size at birth and adiposity: a cohort study. BMC Research Notes 14(1): 160	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Ramakrishnan, U., Grant, F., Goldenberg, T. et al. (2012) Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. Paediatric and Perinatal Epidemiology 26suppl1: 285-301	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because of ineligible country, ineligible study design, or ineligible condition or domain being studied.
Redfern, Kathy M, Hollands, Heidi J, Welch, C Ross et al. (2022) Dietary Intakes of Folate, Vitamin D and Iodine during the First Trimester of Pregnancy and the Association between Supplement Use and Demographic Characteristics amongst White Caucasian Women Living with Obesity in the UK. Nutrients 14(23)	- Ineligible study outcomes *There were no relevant protocol outcomes. Study aimed to investigate dietary and supplementary intakes of vitamin D, iodine and folate in pregnant women with obesity.*
Rolschau, J., Kristoffersen, K., Ulrich, M. et al. (1999) The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. Part I. European journal of obstetrics, gynecology, and reproductive biology 87(2): 105-10; discussion 103	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Shahraki, A. D.; Dehkordi, N. Z.; Lotfizadeh, M. (2016) Comparison of high dose and low dose folic acid supplementation on prevalence, onset and severity of preeclampsia. Advanced Biomedical Research 5: 192	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Iran*
Shaw, G. M.; Velie, E. M.; Schaffer, D. (1996) Risk of neural tube defect-affected pregnancies among obese women. JAMA 275(14): 1093-6	- Ineligible study design *Case-control study*
St-Laurent, Audrey, Plante, Anne-Sophie, Lemieux, Simone et al. (2023) Higher Than Recommended Folic Acid Intakes is Associated with High Folate Status Throughout Pregnancy in a Prospective French-Canadian Cohort. The Journal of nutrition 153(5): 1347-1358	- Ineligible study outcomes *No protocol outcomes. Study reported serum total folate, plasma total vitamin B12, and homocysteine.*
Stamm, R. A., March, K. M., Karakochuk, C. D. et al. (2018) Lactating Canadian Women Consuming 1000 microg Folic Acid Daily Have	- Ineligible population

Study	Code [Reason]
High Circulating Serum Folic Acid Above a Threshold Concentration of Serum Total Folate. Journal of Nutrition 148(7): 1103-1108	*Study assessed serum and blood folate in breastfeeding women taking folic acid*
Stern, S. J., Matok, I., Kapur, B. et al. (2012) Dosage requirements for periconceptional folic acid supplementation: accounting for BMI and lean body weight. Journal of Obstetrics & Gynaecology Canada: JOGC 34(4): 374-8	- Ineligible study outcomes *No protocol outcomes. Study reported recommended folic acid doses for different BMI values*
Van Beynum, I. M., Kapusta, L., Bakker, M. K. et al. (2010) Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: A registry-based case-control study in the northern Netherlands. European Heart Journal 31(4): 464-471	- Ineligible study design *Case-control study*
Vanderlelie J, Scott R, Shibl R et al. (2016) First trimester multivitamin/mineral use is associated with reduced risk of pre-eclampsia among overweight and obese women. Maternal Child Nutrition 12(2): 339-348	- No information on folic acid dose available
Viswanathan, M., Treiman, K. A., Doto, J. K. et al. (2017) Folic Acid Supplementation. Agency for Healthcare Research and Quality: 01	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Wang, H., Mueller, N. T., Li, J. et al. (2017) Association of Maternal Plasma Folate and Cardiometabolic Risk Factors in Pregnancy with Elevated Blood Pressure of Offspring in Childhood. American Journal of Hypertension 30(5): 532-540	- Ineligible population *Study assessed mother-child dyads from birth to 9 years*
Wang, M., Wang, Z. P., Gao, L. J. et al. (2013) Maternal body mass index and the association between folic acid supplements and neural tube defects. Acta Paediatrica 102(9): 908-13	- Ineligible study design *Case-control study*
Wen, S. W., White, R. R., Rybak, N. et al. (2018) Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. BMJ 362: k3478	- Study population has mixed BMI. Outcome data not stratified by BMI>25kg/m^2 or BMI<25kg/m^2.
Wilson, R. D.; Genetics, Committee; Motherisk (2007) Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other	- Ineligible study design *Narrative review reporting a clinical practice guideline*

Study	Code [Reason]
congenital anomalies. Journal of Obstetrics & Gynaecology Canada: JOGC 29(12): 1003-1013	
Wilson, R. D. and O'Connor, D. L. (2021) Maternal folic acid and multivitamin supplementation: International clinical evidence with considerations for the prevention of folate-sensitive birth defects. Preventive Medicine Reports 24: 101617	- Ineligible study design *Narrative review- quality improvement prevention review*
Xie, R. H., Liu, Y. J., Retnakaran, R. et al. (2016) Maternal folate status and obesity/insulin resistance in the offspring: a systematic review. International Journal of Obesity 40(1): 1-9	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because of ineligible country. *All studies conducted in countries other than high income countries (as defined by the OECD)*
Yu, Y., Sun, X., Wang, X. et al. (2021) The Association Between the Risk of Hypertensive Disorders of Pregnancy and Folic Acid: A Systematic Review and Meta-Analysis. Journal of Pharmacy & Pharmaceutical Sciences 24: 174-190	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because of ineligible country and ineligible condition or domain being studied.

Excluded economic studies

No economic study was reviewed at full text and excluded from this review.

Appendix K Research recommendations

Research recommendations for review question: What dose of folic acid supplementation before and during the first 12 weeks of pregnancy is needed for women a BMI ≥ 25 kg/m^2 or more?

No research recommendations were made for this review question.